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Magnetic Resonance Imaging Demonstrates Improved Regional Systolic Wall Motion and Thickening and Myocardial Perfusion of Myocardial Territories Treated by Laser Myocardial Revascularization

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OBJECTIVES This study was designed to investigate the use of magnetic resonance (MR) functional and perfusion imaging to evaluate laser myocardial revascularization (LMR).

BACKGROUND Most clinical studies of LMR have shown improvements in angina class and exercise capacity, with minimal or absent improvements in myocardial perfusion and function.

METHODS Fifteen patients who underwent percutaneous Biosense-guided holmium:yttrium aluminum garnet LMR to areas of viable but ischemic myocardium were followed clinically and underwent functional and perfusion MRI at baseline, 30 days and 6 months.

RESULTS The mean age was 64 ± 11 years; four patients were women. The ejection fraction was 47.4 ± 14.0%. Angina class at baseline was 3.4 ± 0.6 and improved to 2.5 ± 1.4 at six months ($p = 0.054$). Exercise time at baseline was 298 ± 97 s and increased to 350 ± 95 s at 30 days and 365 ± 79 s at six months, $p = 0.04$. There were no significant changes in nuclear perfusion scans. Although MR determined that resting radial motion and thickening of the target wall were significantly less than normal at baseline ($p < 0.001$), they improved significantly during follow-up (wall thickening: baseline, 30.6 ± 11.7%; day 30, 41.2 ± 13.3% and day 180, 44.2 ± 11.9%, $p = 0.01$). The size of the underperfused myocardial area was 14.5 ± 5.4% at baseline and was reduced to 6.3 ± 2.8% at 30 days and 7.7 ± 3.7% at 6 months ($p < 0.001$).

CONCLUSIONS This small phase I, open-label, uncontrolled study of MR functional and perfusion imaging in patients undergoing Biosense-guided LMR suggests a beneficial effect of this treatment strategy on myocardial function and perfusion. The efficacy of Biosense-guided LMR is being evaluated in a large phase II, randomized, blinded placebo-controlled trial with an MRI substudy (DIRECT). (J Am Coll Cardiol 2002;39:1–8) © 2002 by the American College of Cardiology

With the recent approval of the CO_2 (PLC, Franklin, Massachusetts) and holmium:yttrium aluminum garnet (Ho:YAG; Eclipse, Sunnyvale, California) surgical lasers (1), laser myocardial revascularization (LMR) has become a therapeutic option for patients with medically refractory angina who are considered to be suboptimal candidates for standard catheter-based or surgical revascularization strategies (1–5). The Ho:YAG laser's infrared wavelength also allows transmission through optical fibers, making percutaneous catheter-based LMR possible with any of several laser systems under active study (Cardiogenesis, Eclipse and Biosense) (6–8). The proposed mechanisms of LMR benefits include: 1) myocardial perfusion from the left ventricle (LV) through patent laser channels, a hypothesis that is becoming less likely with evidence of early channel occlusion (9–12); 2) new blood vessel growth (myocardial angiogenesis) resulting from release of growth factors and inflammatory mediators (13–17); 3) myocardial denervation leading to reduced symptoms without improved perfusion (18); 4) myocardial fibrosis resulting in a tethering action that improves myocardial function and promotes favorable remodeling; or 5) placebo effect in a highly motivated patient population undergoing a high-tech procedure.

The question is still whether LMR is indeed a form of revascularization strategy, or whether it is only a means of providing symptomatic relief without increasing myocardial perfusion (and without consequent benefits in myocardial function, survival or myocardial infarction, or the need for repeat revascularization, or LV function) (2,12,17,19–21). In fact, most clinical studies of LMR have shown a discrepancy between the significant improvements in angina class and exercise capacity (2,12,14,19,20,22,23) and the minimal or absent improvements in myocardial perfusion

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Abbreviations and Acronyms

ANOVA = analysis of variance
CCS = Canadian Cardiovascular Society
Ho:YAG = holmium:yttrium aluminum garnet
LMR = laser myocardial revascularization
MRI = magnetic resonance imaging
TI = inversion time
TMR = transmyocardial revascularization

and function (24–28). These beneficial effects on perfusion or function are either absent or below the detection limits of currently available imaging modalities (e.g., because of the poor spatial resolution of nuclear perfusion scans and the lack of reproducibility and frequent poor imaging windows of transthoracic echocardiography) (1,2,11,19,21–23,29).

Magnetic resonance imaging (MRI) is an alternative imaging modality that allows serial noninvasive assessment of global and regional myocardial function, the extent of myocardial ischemia using myocardial blood/contrast arrival imaging (30–34) and the extent of myocardial collateralization (35,36). It has been used to investigate the angiogenic potential of several growth factors (30,37–39) but has not yet been used to investigate the "revascularization" effect of LMR. We thus report the 30-day and 6-month results of a pilot MRI evaluation, performed in the recently completed phase I Biosense-guided LMR study, as a prelude to its use in the randomized blinded placebo-controlled phase II Direct Myocardial Revascularization In Regeneration of Endomyocardial Channels Trial (DIRECT) LMR study.

METHODS

Patient selection. The study sample consisted of patients undergoing Biosense electromechanical triangulation guidance system (NOGA)-guided LMR at Boston's Beth Israel Deaconess Medical Center. To be eligible, patients needed to have: 1) an area of myocardium supplied by a major coronary artery with advanced disease not amenable to bypass grafting or percutaneous intervention; or 2) a corresponding area of inducible ischemia (fully or partially reversible defect on a nuclear perfusion scan). They could not have: 1) unstable angina, recent myocardial infarction or recent (three months) coronary angioplasty; 2) ejection fraction <30%; 3) aortic stenosis or sclerosis, or a prosthetic valve; or 4) severe peripheral vascular disease. Additional MRI-specific exclusion criteria included cardiac pacemakers, frequent atrial or ventricular arrhythmias, cerebral metal implants and severe claustrophobia. The study was approved by the Committee for Clinical Investigation of the Beth Israel Deaconess Medical Center. Patients were enrolled between March 1998 and September 1998.

LMR. Patients enrolled in the study underwent LMR using Biosense guidance. This NOGA system allows accurate on-line localization of the catheter tip within the LV, map (40–42) relative to three location pads that are positioned under the subject's back and emit an ultralow (10^{-6}-10^{-5}Tesla) magnetic field. The intensity of the three magnetic fields is detected by miniature antennae within the tip of a deflectable catheter, providing precise spatial localization after triangulation within a Silicon Graphics workstation. As the catheter is placed sequentially against the LV endocardial surface at a series of points, the local unipolar electrogram and tip motion during the cardiac cycle are recorded. This allows calculation of unipolar voltage and local wall shortening (percent change in the average distance between a point and its neighbors from end-diastole to end-systole) at each such point. A three-dimensional map of each parameter can be displayed and rotated freely in space to inspect all LV walls. Areas of reduced local unipolar voltage and reduced local shortening indicate scar; areas of preserved local unipolar voltage and reduced local shortening indicate severe resting ischemia (40–42). Following diagnostic mapping, a second catheter with the same tip sensor and a laser fiber is used to administer Ho:YAG laser pulses (2 J) to the ischemic areas indicated on the baseline NOGA map. Fifteen to 25 laser channels are performed in each ischemic area, up to a maximum of two zones (Fig. 1).

Follow-up. Patients were followed for six months following the index procedure. Transthoracic echocardiograms were performed at baseline, 24 h following the index procedure and at one month of follow-up. Patients were followed for six months for death, myocardial infarction, need for repeat revascularization and angina class (43). Exercise treadmill testing and rest thallium-adenosine sestaMIBI nuclear perfusion scans were performed at baseline, 30 days and 6 months following LMR. Nuclear scans were subjected to core laboratory analysis using a semiquantitative segmental analysis and an automated quantitative analysis. In addition, left ventriculography, coronary angiography and Biosense NOGA mapping were performed at baseline to guide therapy and then at six months of follow-up. Clinical follow-up of at least six months was available on all patients.

MRI. Magnetic resonance imaging was performed at baseline, and at 30 days and 6 months. MRI was performed in the body coil of a 1.5 Tesla whole-body Siemens Vision system. Functional imaging was performed during breathhold using shared-center FLASH cine imaging in each of the three mutually perpendicular views comprising biplane long axis and a stack of short-axis views, with short axis imaged from base to apex in contiguous sections 0.5 cm thick, collected over approximately 12 heartbeats to measure regional wall systolic thickening and motion. Magnetic resonance blood arrival imaging was assessed, as previously described (30,37). A series of four inversion recovery images were obtained with the inversion time (TI) adjusted to minimize signal intensity from myocardium. Using the best TI for nulling myocardial signal, a series of concurrent parallel images were acquired in diastole during breathhold, at baseline and after the bolus injection of contrast media (0.05 mmol/kg gadodiamide) (30,34,44). For perfusion imaging, three slices were obtained in each patient.

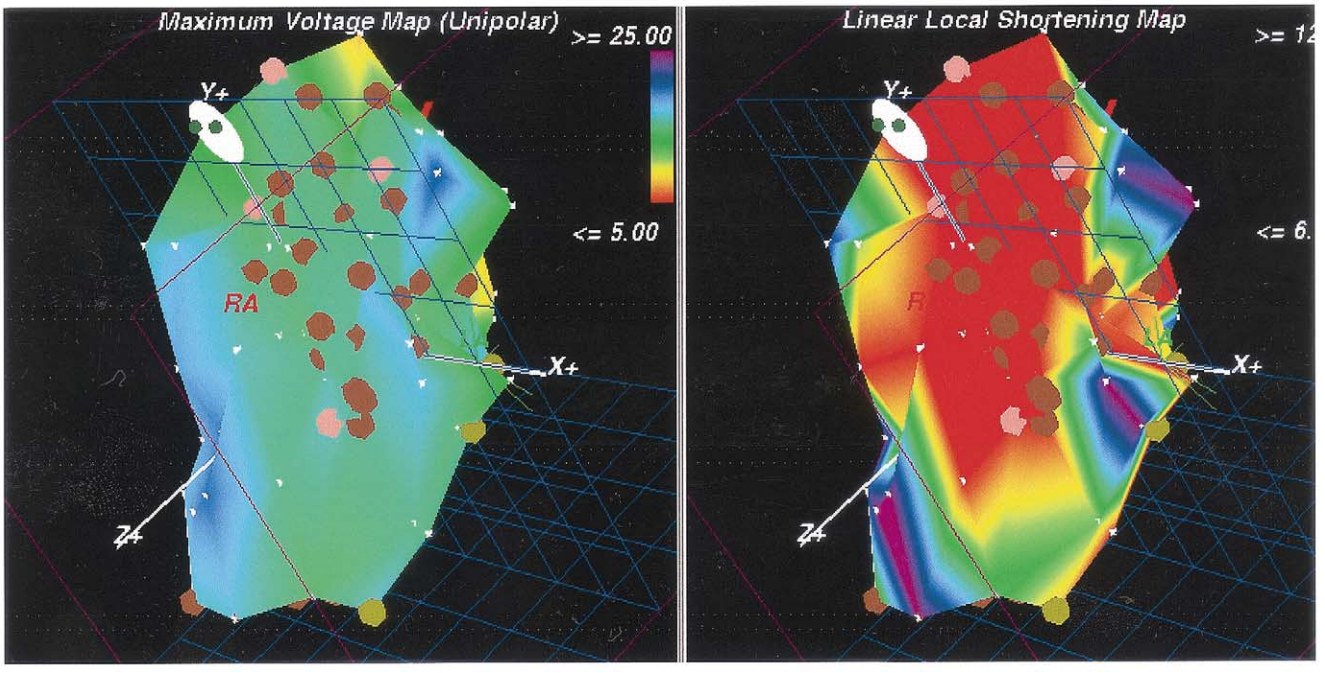

Figure 1. Left anterior oblique cranial Biosense NOGA unipolar **(left)** and linear local shortening map **(right)** shows reduced anterolateral wall linear local shortening in **red** (regional function) with preserved unipolar voltage indicating viable but underperfused myocardium. Twenty-five laser channels were created using the Biosense Ho:YAG laser system **(brown dots)** in the "ischemic" zone **(red)** of the anterolateral wall.

Measurement of the timing of half-maximum signal arriving in the different parts of the myocardium demonstrated the existence of several distinct regions including normal myocardium and areas exhibiting delayed contrast arrival (underperfused zones). For each scan, a space-time map demonstrating distribution of contrast signal density over the LV wall as a function of time was created. The extent of the territory demonstrating delayed arrival of contrast, defined as >1 s delay of contrast density reaching its 50% maximum value reflecting the most severely hypoperfused part of the myocardium, was then calculated and expressed as percent of the total LV myocardial area (30). If more than one area was treated, the extents of delayed contrast arrival zone in both areas were measured. Magnetic resonance analysis was performed in a semiautomated fashion by a core lab blinded to study sequence.

Statistical methods. Data are expressed as mean ± standard deviation. The changes in the exercise treadmill test time and MR measurements were evaluated using two-way repeated-measures analysis of variance (ANOVA). In addition, measurements at 30 days and 6 months were compared to baseline using paired Student *t* test. All reported p-values were two-tailed, and a p-value ≤0.05 was considered statistically significant.

RESULTS

Patient population. Nineteen patients met all eligibility criteria for the Biosense Phase I LMR study and were treated at Boston's Beth Israel Deaconess Medical Center. Of these patients, 15 patients underwent MRI exclusion (pacemaker in 1 patient, unavailability of the magnet in 2 patients and claustrophobia in the fourth patient) and are the focus of this study. The baseline characteristics are presented in Table 1. The mean age was 64 ± 11 years (range 38 to 77 years) with four women. Seven patients (46.7%) had diabetes mellitus, 13 patients (86.7%) had hypertension and 14 patients (93.3%) had prior coronary artery bypass grafts. The mean ejection fraction (evaluated by left ventriculography) was 47.4 ± 14.0% (range 30% to 73%). Fourteen patients (93.3%) had Canadian Cardiovascular Society (CCS) Class III or IV angina.

Table 1. Baseline Clinical Characteristics

	Patients (n = 15)
Age (range)	64.1 ± 11 (42–77)
Men/women	11/4
Diabetes mellitus	7 (46.7%)
Hypertension	13 (86.7%)
History of elevated cholesterol*	14 (93.3%)
Prior CABG	14 (93.3%)
Current tobacco use	4 (26.7%)
Prior PTCA	8 (53.3%)
Prior CVA/TIA	2 (13.3%)
Prior myocardial infarction	9 (60%)
Canadian Cardiovascular Society	
Class III	7 (46.7%)
Class IV	7 (46.7%)
Ejection fraction by left ventriculography (range)	47.4 ± 14.0 (30–73)

*Serum cholesterol >200 mg/dl.

CABG = coronary artery bypass grafting; CVA/TIA = cerebrovascular accident/transient ischemic attack; EF = ejection fraction; PTCA = percutaneous transluminal coronary angioplasty; MR = magnetic resonance imaging.

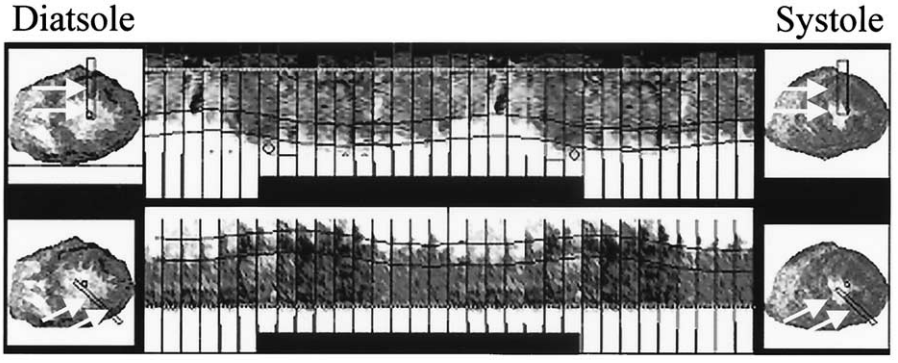

Figure 2. Functional imaging was performed during breath-hold using shared-center FLASH imaging producing 16 to 24 sequential image frames each (cine MR), collected over approximately 12 heartbeats to measure regional wall systolic thickening and motion. The target wall(s) was interrogated **(arrow)** using an automated algorithm and displayed as a function of time allowing the determination of target wall motion and thickening.

Acute results and intermediate-term follow-up. After NOGA mapping, the delineated target treatment area was 22 ± 11% of the endocardial surface area as judged by the maps. Biosense-guided LMR was performed with 32 ± 9 laser channels (range 17 to 49 channels with a mean channel density 1.1 ± 0.6 channels/cm^2 within the treatment zone, Fig. 1). The procedure was successful in all patients and there were no acute procedural complications (death, myocardial infarction, emergent revascularization, LV perforation or stroke). At six months of follow-up there were no deaths, Q-wave myocardial infarctions or repeat revascularizations. One patient had a non–Q-wave myocardial infarction at three months. The mean angina class (CCS) at baseline was 3.4 ± 0.6 and improved to 2.5 ± 1.4 at six months ($p = 0.054$). The mean exercise time was 298 ± 97 s at baseline, 350 ± 95 s ($p = 0.11$) at 30 days, and 365 ± 79 s ($p = 0.02$), at 6 months (ANOVA, $p = 0.04$). There were no significant changes in nuclear perfusion scan stress sum scores, redistribution score or rest sum scores as assessed by core laboratory analysis.

MRI. LEFT VENTRICULAR FUNCTION ASSESSMENT. Magnetic resonance imaging was performed in all 15 patients at baseline and was repeated at day 30 ($n = 13$) and at six months ($n = 15$). Each scan assessed resting ejection fraction, resting regional wall motion and thickening and myocardial contrast arrival. Systolic radial motion and thickening of the target area (treated area) and normal wall (best function) were measured using a semiautomated quantification algorithm of short-axis MR images (Fig. 2). Overall LV function was 48.8 ± 11.4% at baseline, similar to the left ventriculography assessment (47.4 ± 14.0%, $p = 0.76$). There was a trend towards slight improvement in LV function at day 180 (day 30 ejection fraction 52.3 ± 11.8% and day 180 ejection fraction 56.1 ± 12.7%), which did not reach statistical significance ($p = 0.25$).

Resting baseline thickening (45.3 ± 11.5%) of the normal wall did not change significantly throughout the study, but there was a trend towards improvement of normal wall systolic radial motion (from 22.8 ± 9.4% to 25.8 ± 9.4% at 30 days, and 30.8 ± 3.9% at 6 months, ANOVA $p = 0.02$, Fig. 3). Resting radial motion and thickening of the target wall were significantly less than that of the normal wall at baseline ($p < 0.001$, Fig. 3), and improved significantly at 30 days and 6 months. The improvements in target wall thickening (baseline, 30.6 ± 11.7%; day 30, 41.2 ± 13.3%, $p = 0.03$; and day 180, 44.2 ± 11.9%, $p = 0.003$, ANOVA $p = 0.01$, Fig. 3, top), and target wall motion (baseline, 16.3 ± 9.2%; day 30, 21.8 ± 9.5%, $p < 0.01$; and day 180, 25.3 ± 7.3%, $p = 0.006$, ANOVA $p = 0.02$, Fig. 3, bottom) were both statistically significant at day 180.

MYOCARDIAL PERFUSION/CONTRAST ARRIVAL ASSESSMENT. Myocardial perfusion/contrast arrival was assessed using MRI (Fig. 4). The mean size of the delayed contrast arrival zone (underperfused area of the myocardium) was 14.5 ± 5.4% of the LV at baseline. The size of the myocardial area demonstrating delayed contrast arrival, corresponding to the laser-treated group, was reduced significantly (ANOVA $p < 0.0001$) at day 30 (6.3 ± 2.8%, $p < 0.001$) and day 180 (7.7 ± 3.7%, $p < 0.001$), as compared to baseline. There was no correlation between the density or number of laser channels used and the improvement in regional wall function or extent of improvement in myocardial hypoperfusion.

DISCUSSION

In this phase I trial of Biosense-guided LMR, the main intent was to demonstrate the safety and feasibility of this treatment strategy. In the small group of patients enrolled at our single center, the treatment was safe and was associated with improvement in both angina class and exercise capacity. Although there was no demonstrable improvement in nuclear perfusion scans, assessment of MR perfusion/contrast arrival demonstrated a concomitant reduction of the size of the underperfused area within the treated zones. Magnetic resonance imaging also showed an improvement in regional wall radial motion and systolic thickening of the laser-treated myocardial regions, whose regional function had been reduced at baseline. Assessment of MR perfusion/contrast arrival demonstrated a concomitant reduction of the size of the underperfused area within the treated zones. This study is thus the first demonstration of specific

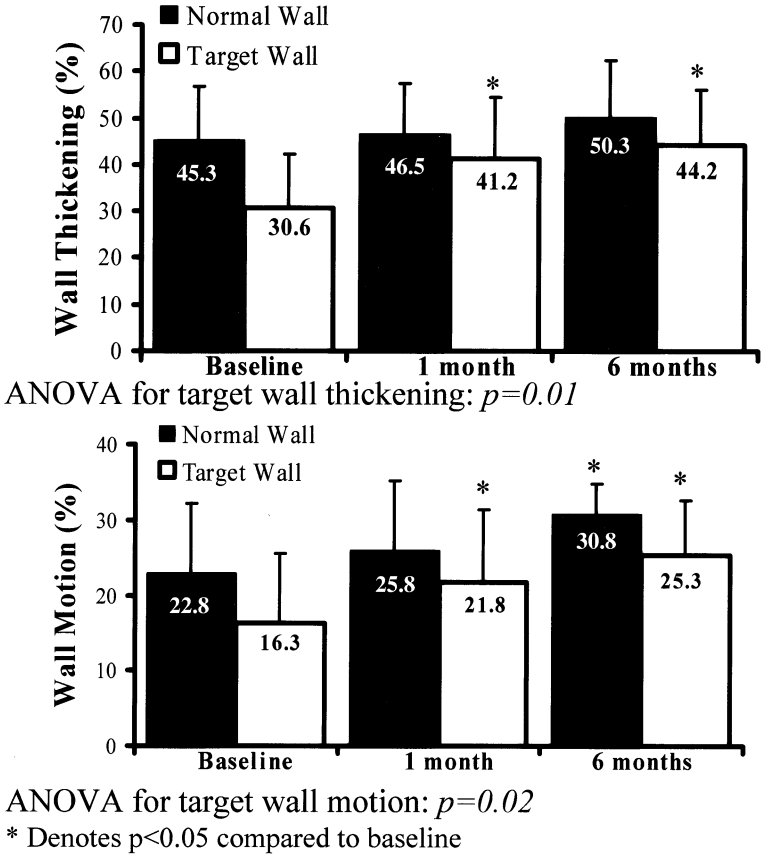

Figure 3. Resting normal **(black bars)** and target **(white bars, treated)** wall thickening **(top)** and radial wall motion **(bottom)** showed improvement in the target wall function at 30 and 180 days. In addition, there was a significant improvement in normal wall motion at 180 days. *Statistical significance with a $p < 0.05$ by paired t test. ANOVA = analysis of variance.

improvement in function and "perfusion" of the laser treated zones.

Although the small sample size, the absence of a control group and the absence of a correlation with the number and density of laser channels preclude any definitive conclusions regarding efficacy, these findings of improved perfusion and function in the treated segments would support a potential revascularization mechanism for LMR. On the other hand, the concomitant improvements in normal wall motion and trend for overall improvement in LV ejection fraction may suggest a role of improved cardiac conditioning, which could be related to nonspecific "cardiac rehabilitation effect" after relief of angina by any mechanism, including a placebo effect. However, this could be attributed to favorable remodeling after LMR. Treatment-specific benefit can only be demonstrated within a blinded placebo-controlled study of LMR, as will be possible from the MRI substudy of the 300-patient DIRECT study.

It should also be pointed out that although cardiac MRI is considered the "gold standard" for evaluation of LV function (31,45), its application to clinical trials in coronary disease to date is very limited (46). Similarly, despite recent advances in magnetic resonance-based perfusion assessment of the myocardium (30,44,47,48), there has been no substantial clinical experience with this imaging modality (49). In prior animal studies, we have documented improvement in magnetic resonance-assessed parameters of LV function in the setting of angiogenic growth factor therapy (30,38,50). In addition, the newly developed variation of MR perfusion imaging that relies on generation of space-time maps proved capable of detecting changes in coronary perfusion in a pig ameroid model (30,38) and proved capable of detecting improved regional myocardial perfusion in patients (37).

Comparison to prior clinical trials of LMR. These data shed important light on other recently reported (non-blinded) trials of LMR. A phase II study of surgical transmyocardial laser revascularization (TMR) versus medical therapy enrolled 275 patients followed for one year (51). Angina, exercise tolerance and quality-of-life scores were significantly higher in the transmyocardial-revascularization group than in the medical-therapy group, with no differences in myocardial perfusion between the two groups, as assessed by nuclear imaging (51). A second study enrolled 182 patients and randomized them to continued medical therapy versus surgical TMR (24). At 12 months, again exercise tolerance, angina and quality of life assessment were significantly improved in the TMR group as compared with the medical treatment group, without improvement in nuclear perfusion (24). A third randomized study of surgical

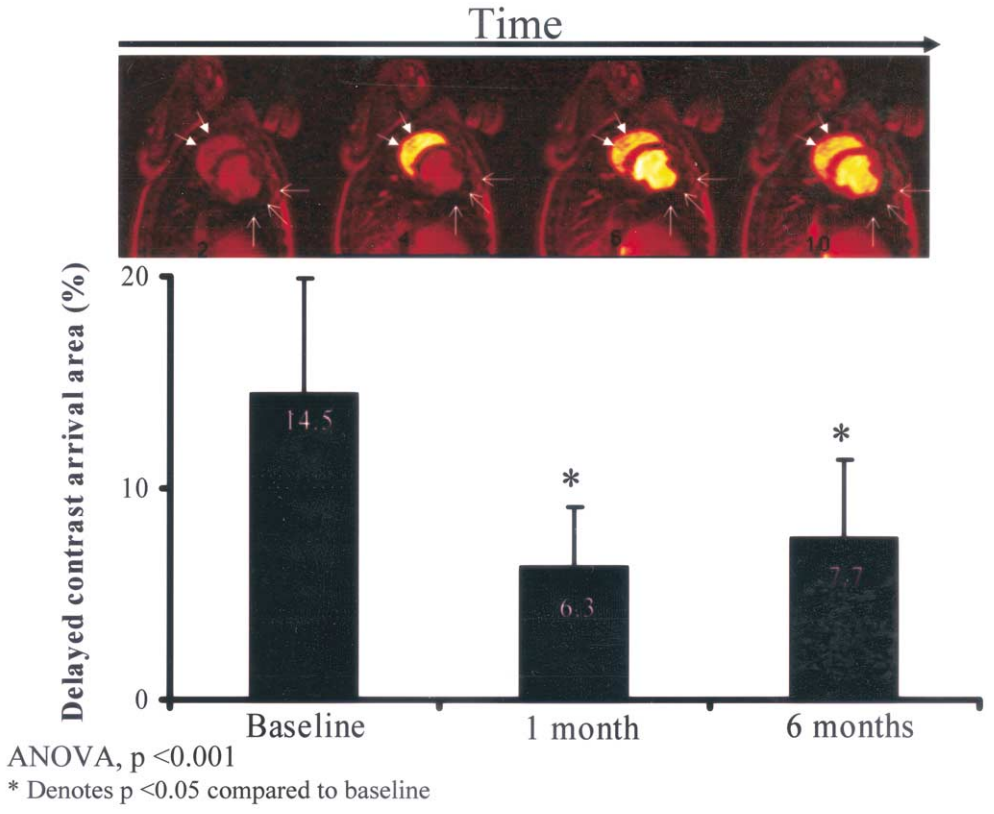

Figure 4. Myocardial perfusion/contrast arrival was assessed using MR imaging after bolus administration of gadodiamide, an MR contrast agent. Time sequence display of selected short axis diastolic images **(top)** shows contrast arrival to the right ventricle **(closed arrow)**, then to the left ventricle **(open arrow)**, followed by the left ventricular myocardium. The mean size of the delayed contrast arrival zone (underperfused area of the myocardium) was 14.5 ± 5.4% of the left ventricle at baseline. The size of the myocardial area demonstrating delayed contrast arrival was reduced significantly at one and six months, as compared to baseline. *Statistical significance with a $p < 0.05$ by paired t test. ANOVA = analysis of variance.

TMR versus medical therapy enrolled 192 patients and showed improved angina, quality of life and myocardial perfusion as assessed by nuclear perfusion imaging in the TMR group as compared to medical therapy (52). A fourth randomized study of TMR versus medical therapy enrolled 100 patients and showed improvement in angina and exercise capacity without any significant change in nuclear perfusion scans in the TMR group as compared to medically treated patients. Thus, most clinical studies of LMR have shown significant improvements in angina class and exercise capacity (6,7,24,25,27,28,51–53), with most studies showing no significant or consistent improvement in perfusion and myocardial function (24–28). Therefore, these beneficial effects are either not present or cannot be detected with currently available imaging modalities. The poor spatial resolution of nuclear perfusion scans and the lack of reproducibility and frequent poor imaging windows of transthoracic echocardiography have been blamed for the lack of demonstrable improvement in perfusion and function (6,7,24,25,27,28,51–53).

In the current study, MR appears to be a promising novel imaging modality that may circumvent these limitations. Its application in our patient cohort suggested a beneficial effect of LMR on both perfusion and function. This is particularly important because demonstrating a true revascularization effect (improved perfusion and function) will be crucial to acceptance of this treatment strategy in patients with severe ischemic heart disease, particularly absent objective evidence of hard clinical benefit (enhanced survival, freedom from cardiac adverse events).

Conclusions. This small phase I open-label study using MRI in patients undergoing Biosense-guided LMR suggests a beneficial effect of this treatment strategy on myocardial perfusion and function. The efficacy and safety of Biosense-guided LMR is currently being evaluated in a large phase II, randomized, blinded placebo-controlled trial with an MRI substudy (DIRECT).

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